MAR 1 4 2014

510(k) Summary: FREND™ TSH

510(k) Number:

K131928:

Summary Preparation Date:

March 13, 2014

Submitted by:
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Proprietary Names:

FREND™ TSH

Common Names:
Quantitative TSH Immunoassay

Regulatory Information:

Regulation section:
862.1690 Radioimmunoassay, Thyroid Stimulating Hormone

Classification:
Class II

Panel:
Chemistry and Toxicology (DCTD))

Product Code(s):
JLW Radioimmunoassay, Thyroid Stimulating Hormone

Other codes used by predicate devices:
None

Predicate Devices:
TOSOH ST AIA-PACK TSH (K972586)

Indications for Use:

510(k) Number:
K131928

Device Name:
FREND™ TSH

Indications for Use:

FREND™ TSH is designed for *in vitro* DIAGNOSTIC USE ONLY for the quantitative measurement of Thyroid Stimulating Hormone (thyrotropin or TSH) in human serum and lithium heparin plasma using the FREND™ system.

FREND™ TSH is indicated for use in clinical laboratories upon prescription by the attending physician as an aid to clinicians in the diagnosis of thyroid disease.

Technological Characteristics:

There are no technological characteristics of FREND™ TSH that are different or with which the agency is unfamiliar. FREND™ TSH, performed using the FREND™ system, is an *in vitro* diagnostic test for the quantitative measurement of TSH in serum and lithium heparin plasma samples. The FREND™TSH is performed completely within the single-use plastic cartridge once serum or plasma has been placed in the sample well and is for use upon prescription by the attending physician in clinical laboratories with qualified technologists. FREND™ TSH on the FREND™ system has been shown to yield TSH results that are equivalent to those obtained with other previously cleared FDA *in* vitro diagnostic devices measuring TSH quantitatively in serum and/or plasma.

The FREND™ System is a bench top fluorescence reader containing a simple computerized touchscreen user interface, easily manipulated to order tests, display results and operate the mechanical functions of the instrument. The specimen is

added with a transfer pipette to the sample inlet of a single use cartridge by the operator, allowing the appropriate volume of sample (35 µL) to be delivered into the FREND™ TSH cartridge. The cartridge is then placed into the FREND™ system, which is programmed to begin analysis once the sample has reacted with the reagents. All reactions occur in the self-contained plastic cartridge and the reading is done in the cartridge as well. The FREND™ system has a slot that accepts the FREND™ TSH test cartridge containing the reagents and sample, and is programmed to analyze the test when the sample has fully reacted with the on-board in-cartridge reagents. Cartridges are loaded manually one by one by the operator. The reaction and analysis time is approximately 5 minutes. TSH quantitation is based on the ratio of fluorescence detected by the FREND™ System at the FREND™ TSH test and reference windows in the plastic cartridge compared to a standard curve stored in the TSH Code Chip that is included with each box of the device. A higher ratio of fluorescence is indicative of a higher TSH concentration. In other words, the magnitude of the fluorescent ratio is directly proportional to the amount of TSH in the sample. A high-level schematic and process diagram of the FREND™ system are included in the User Manual. Results of the test are displayed on the screen and can be printed on an optional printer.

Expected Values

As with every clinical diagnostic test, a reference interval corresponding to the characteristics of the population being tested should be determined by each laboratory. Historically, it has been shown that there are neither racial differences nor gender differences in the reference interval for TSH so creating a single adult reference interval is reasonable and justified per literature.

During a clinical study run to support the FREND™ TSH substantial equivalence to a marketed product with the same indication, TSH measurements were performed on the serum of 385 apparently healthy ambulatory adults (195 males and 191 females ages 18 – 71) who stated they had no known thyroid conditions. All samples were assayed in singlicate on the FREND™ TSH and the predicate device. A single value, determined as an outlier in both the test and the predicate devices, was removed from the data set after which a non-parametric reference interval encompassing the central 95% of the results was determined. Male and female results were separately analyzed with no significant difference found in the calculated reference intervals. Therefore, a single reference interval has been determined.

FREND™ TSH Reference Interval:	0.49 ~ 3.82 mIU/L

With 90% confidence limits the following ranges were estimated:

Lower Reference Interval Range	0.42 ~ 0.59 mIU/L
Upper Reference Interval Range	3.24 ~ 4.30 mIU/L

As in all *in vitro* diagnostic testing, a TSH result generated using the FREND™ TSH on the FREND™ system should be interpreted in the light of other clinical findings and diagnostic procedures. Any TSH results not correlating with the clinical condition should be repeated and other testing performed to clarify the situation.

Performance Characteristics

Performance characteristics were evaluated for FREND™ TSH as follows:

1) Accuracy

1a) Dilution Linearity - Specimens from a high TSH concentration pool were diluted with a TSH depleted serum pool according to the CLSI EP06-A document. Linearity was demonstrated from <0.06 mIU/L to 25.54 mIU/L (Slope = 0.977, y-Intercept = 0.17, $S_{y/x}$ = 0.28, r = 0.999). Correlation with the expected linearity was excellent showing less than the allowable non-linearity. Performance requirement was verified over the measurement interval.

FREND™ TSH is linear from 0.06 ~ 25.0 mIU/L

Figure 1

FREND™ TSH Linearity

% Level	Rep. 1	Rep. 2	Rep. 3	Mean	Linear Fit
0	0.01	0.01	0.03	0.017	0.173
10	2.85	2.78	2.78	2.803	2.714
20	5.61	5.37	5.47	5.483	5.255
30	8.47	7.80	8.53	8.267	7.796
40	9.60	9.43	10.62	9.883	10.337
50	12.2	13.17	12.51	12.627	12.878
60	15.63	15.64	14.27	15.180	15.418
70	18.72	17.43	17.63	17.927	17.959
80	21.88	20.09	20.37	20.780	20.500
90	22.38	23.37	23.68	23.143	23.041
100	25.91	25.32	25.40	25.543	25.582

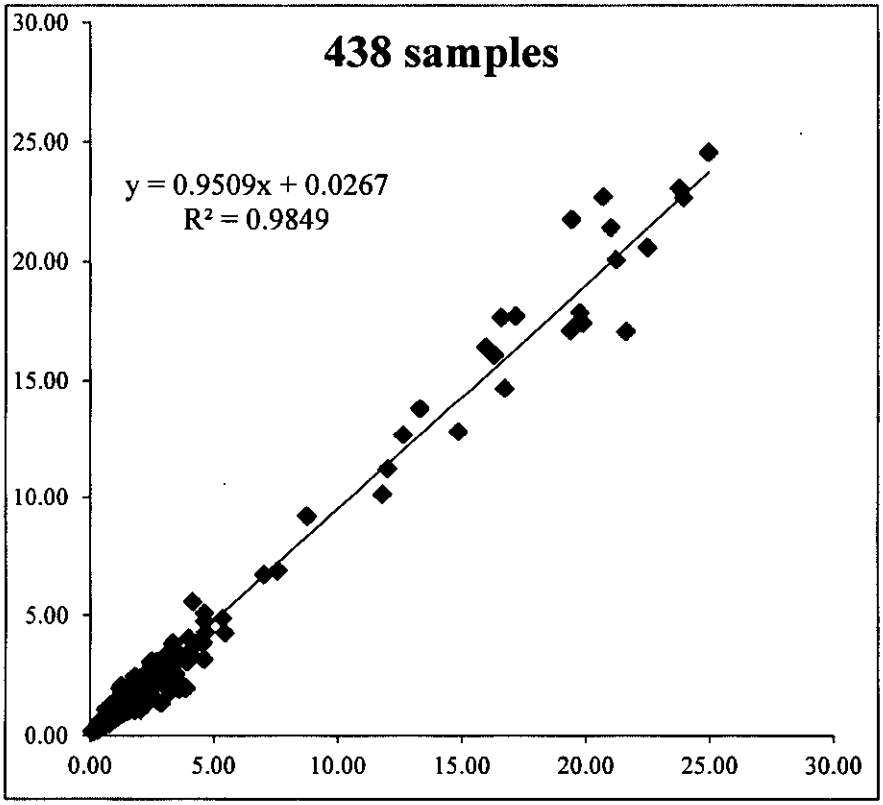
Non-linearity is less than allowable non-linearity: 20% up to 1 mIU/L then 10%.

1b) Comparative Analysis - 438 serum samples obtained from subjects both apparently normal and with thyroid conditions as well as other undisclosed diseases and conditions and stored at -70° C under monitored conditions for less than one year, were analyzed using both the FREND™ TSH and another commercially available TSH fluorescent immunoassay. Results generated using the FREND™ TSH on the FREND™ System (y) were compared to those obtained using a previously FDA cleared TSH assay (x). Results of this study are shown below:

Slope: 0.951 (95% CI: 0.940; 0.962)
y-Intercept: 0.0266 (95% CI: -0.0258; 0.0790)
$S_{y/x}$: 0.475
Number of Samples: 438
Measuring Range: 0.09 ~ 24.96 mIU/L

Comparability using CLSI guideline EP09-A2-IR, Section 7, shows that the difference in concentration between that measured by the test device and that expected (predicate device) is less than the allowable difference and that the two methods compare favorably.

Figure 2
Comparability to Predicate Device



2) Precision

Precision was determined as described in the CLSI protocol EP05-A2. Four clinical samples were assayed in replicates of two at two separate times per day for twenty days using a single lot of FREND™ TSH cartridge. The findings follow showing repeatability, between-run, between-day and within-laboratory precision data.

Figure 3

FREND™ Single Site Single Lot Precision

Sample	Mean TSH	Repeatability		Between-run		Between-day		Within-laboratory	
	Conc. (mIU/L)	SD (mIU/L)	CV%	SD (mIU/L)	CV%	SD (mIU/L)	CV%	SD (mIU/L)	CV%
1	0.496	0.043	8.6	0.012	2.4	0.017	3.4	0.047	9.6
2	5.948	0.353	5.9	0.082	1.4	0.031	0.5	0.364	6.1
3	11.989	0.555	4.6	0.375	3.1	0.156	1.3	0.688	5.7
4	23.763	0.846	3.6	0.478	2.0	0.000	0.0	0.972	4.1

3) Specificity

The α- subunits of luteinizing hormone (LH), follicle stimulating hormone (FSH), human chorionic gonadotropin (hCG) and thyroid stimulating hormone (TSH) are all very similar though their β- subunits are not. Because of the structural similarities, the specificity of the FREND™ TSH must be examined in the presence of large amounts of these possible cross-reactants. The following substances were evaluated for potential cross-reactivity with the FREND™ TSH at the concentrations indicated below in Figure 4. Testing was done according to the CLSI protocol EP07-A. No significant cross-reactivity was found.

Figure 4
Specificity of FREND™ TSH

Sample TSH Conc. (mIU/L)	Interferent	Material added	% Cross Reactivity
0.49	hCG	200,000 mIU/mL	2×10^{-8}
0.55	LH	500 mIU/mL	2×10^{-4}
0.55	FSH	500 mIU/mL	-5×10^{-6}
6.22	hCG	200,000 mIU/mL	3×10^{-7}
6.06	LH	500 mIU/mL	3×10^{-5}
6.06	FSH	500 mIU/mL	1×10^{-4}

4) Analytical Sensitivity

The Limit of Detection (LoD) for the FREND™ TSH was measured using the CLSI EP17-A protocol. The analytical sensitivity of the FREND™ TSH was determined to be 0.06 mIU/L.

5) Interference

Interference is defined in this instance as recovery outside of 10% of the known specimen mean concentration. In other words, recovery from 90% to 110% of the expected TSH is considered acceptable performance. The interference studies were performed using the recommendations in the CLSI EP07-A protocol. Results were:

Endogenous Interferents

- Added hemoglobin (up to 500 mg/dL) does not interfere with the assay. Average TSH recovery was 98.8%.
- Added conjugated bilirubin (up to 20 mg/dL) does not interfere with the assay. Average recovery was 100.0%.
- Added total protein up to 12.0 g/dL does not interfere with the assay. Average recovery was 100.4%.
- Added triglyceride up to 3 g/dL does not interfere with this assay. Average recovery was 101.6%.

- Added HAMA to 52.5 ng/mL did not interfere with the assay. Average recovery was 93.3%. Higher concentrations of HAMA exhibited interference> 10%.

- RF at 53.8 IU/mL did not interfere with the assay. Average recovery was 91.4%. Higher concentration of RF did show interference > 10%.

Pharmaceutical Interferents

The following common medications were tested for interference with the FREND™ TSH. The testing showed no significant interference (<10%) from the tested drugs at the listed concentration that would affect the interpretation of a TSH result as assayed on the FREND™ TSH:

Figure 5

Interference from Common Medications

Tested Drug	Concentration Tested (µM)
Acetaminophen	1324
Diltiazem	15
Erythromycin	81.6
Verapamil	4.4

6) High Dose Hook Effect Testing (Prozone Detection)

No High Dose Hook effect was seen in samples with a TSH concentration as high as 2500 mIU/L.

7) Reagent Stability Studies

Reagent stability studies based on procedures and criteria in the NanoEnTek quality system showed that the cartridges for FREND™ TSH are good for at least one year from the date of manufacturer if stored refrigerated appropriately as directed. Stability of the cartridges at room temperature (22~28°C) was found to be six months.

8) Matrix Study

TSH concentrations in 40 sample pairs, each with serum and lithium heparin plasma aliquots, were measured using the FREND™ TSH. Linear regression analysis of serum results (x) compared to lithium heparin plasma results (y) yielded the following equation ($r = 0.992$, $r^2 = 0.985$), indicating FREND TSH can be measured equally well in serum and lithium heparin plasma:

$$y = 0.995x - 0.320$$

CLIA '88 - Complexity Categorization.

NanoEnTek has a previous reagent cartridge assay cleared by 510(k) in the US and this has been assigned a moderate complexity classification. The predicate TSH device is also marketed as a MODERATE complexity device. The logical assumption is that the FREND™ TSH does not require a high complexity classification and there is a valid argument because of the ease of use for assigning the FREND™ TSH a MODERATE COMPLEXITY categorization.

Substantial Equivalence

NanoEnTek has developed the FREND™ TSH for the FREND™ system and completed the necessary analytical and clinical validation studies to demonstrate the performance characteristics of the test for use as supporting data for this 510(k) premarket notification and for its claim of substantial equivalence.

In conclusion, the performance study results summarized below support the claim of substantial equivalence of the FREND™ TSH to the Predicate Device. Detailed data is filed in the 510(k) documentation.

Figure 6

Comparative Characteristics: FREND™ TSH and Predicate Device

Similarities

Items	Device	Predicate
	FREND™ TSH	ST AIA-PACK TSH
510(k) Number	K131928	K972586
Regulations	862.1690 Radioimmunoassay, Thyroid Stimulating Hormone	Same
Product Code	JLW	Same
Device Class	II	Same
Intended Use	Quantitative measurement of TSH	Same
Indications for Use	To quantitatively measure TSH in serum, heparin plasma	Same
Warnings and Precautions	For use in clinical laboratories upon prescription by the attending physician	Same
Contra-indications	Should not be used to measure TSH in patients who have received therapeutic doses of mouse monoclonal antibody therapeutics. Not to be used for newborn screening.	Same
Similar Assay Sensitivity (LoD)	Measured at 0.06 mIU/L	Measured at 0.03 mIU/L

Items	Device	Predicate
	FREND™ TSH	ST AIA-PACK TSH
Interference from Drugs	No interference found in the drugs that were tested at the concentrations they were tested.	Same
Test Vessel	Disposable single-use reaction vessel	Same
Sample Type	Serum and lithium heparin plasma	Same
Sample Prep	Prepare serum/plasma from whole blood	Same
Quality control	Internal procedural/instrument quality controls; External QC at normal and elevated levels.	Same
Interpretation of Results	Comparing fluorescence for sample against a standard calibration curve	Same
Reaction Type	Antibody/antigen complexes	Same
Type of Test	Fluorescent immunoassay detecting TSH	Same
Sample Carry-over	None detected – single use cartridge	Same- single use cup
Endogenous Interference	None by Bilirubin, Triglyceride, Cholesterol, Total Protein detected in testing performed	Same
End Users	Technologists working in a clinical laboratory	Same
Result Comparability	Results across the range of 0.09 – 24.96 mIU/L equivalent between ST AIA-PACK TSH and FREND™ TSH	Same
Reference Int.	0.49 – 3.82 mIU/L	0.47- 4.09 mIU/L

Figure 7

Comparative Characteristics: FREND™ TSH and Predicate Device

Differences

Items	*Device*	*Predicate*
	FREND™ TSH	**ST AIA-PACK PA**
Random Access/ Degree of Automation	No random access, mainly manual manipulation	Random access, semi-automated
Test Throughput	Single Test 5 minutes to result.	Single test 18 minutes; 50 tests 68 minutes.
Calibration Standard	WHO International Standard Hormone, hormone for immunoassay, NIBSC code: 81/565	WHO 2nd International Reference Preparation 80/558 (1983)

Figure 8 - Summary

Performance Validation Studies Supporting Substantial Equivalence

No.	Study	Summary of Results
1.	Analytical Sensitivity/ Limit of Detection (LoD)	FREND™ TSH Limit of Detection (LoD) was determined to be 0.06 mIU/L. Sensitivity on the predicate device is listed as being 0.03 mIU/L. Similar sensitivity limits.
2.	Interfering Substances	The FREND™ TSH was tested for interference with endogenous materials such as hemoglobin, bilirubin, triglycerides, and total protein, at levels equivalent to those tested by the predicate device. Neither assay showed clinically significant interference.
3.	Specificity	Specificity testing with biological substances with similar structures (LH, FSH, βHCG) was performed and showed insignificant interference with both the test and predicate devices.
4.	Carry-over	Both the test system and the predicate system use disposable pipette tips and an individual reaction vessel to prevent possible carryover.
5.	Reference Intervals	Independent Reference Intervals were calculated for both the test and predicate devices using the same pool of apparently healthy subjects. The Reference Interval for both methods was determined to be approximately 0.5 – 4.0 mIU/L
6.	Comparability	438 samples were analyzed on both devices – the TOSO ST AIA-PACK™ TSH and the FREND™ TSH. Descriptive statistics for the comparability show equivalent performance. Thyroid status was equivalent between methods 98.4% of the time in the study.
7.	Precision	Precision Material testing demonstrated acceptable performance throughout the measurement range of the assay for both test and predicate devices.

Overall Conclusions from the Document

The information and data in this 510(k) document demonstrate that the FREND™ TSH is an accurate, reliable test that correlates well with current cleared methods for the quantitation of serum and lithium heparin plasma

TSH. The contents of this submission demonstrate that the FREND™ TSH on the FREND™ system is substantially equivalent to its predicate device and, therefore, safe and effective for its intended use, measuring quantitatively TSH in human serum and lithium heparin plasma.

Substantial Equivalence Conclusions

The FREND™ TSH is as safe and effective as the "Predicate Device", the TOSOH ST AIA-PACK™ TSH assay. FREND™ TSH has a similar Intended Use and Indications for Use: the quantitative measurement of TSH in serum and heparinized plasma, similar technological and performance characteristics, and principles of operation as its predicate device. The differences between the FREND™ TSH and its predicate device raise no new issues of safety or effectiveness. Performance data, analytical and clinical, demonstrate that the FREND™ TSH is as safe and effective as the "Predicate Device". Thus, the FREND™ TSH must be found to be substantially equivalent to the TOSOH ST AIA-PACK TSH.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

March 14, 2014

NANOEN TEK USA, INC.
C/O JUDITH LOEBEL
DOCRO
1 JACKS HILL ROAD, SUITES A & B
OXFORD CT 06478

Re: K131928
Trade/Device Name: FREND™ TSH
Regulation Number: 21 CFR 862.1690
Regulation Name: Thyroid stimulating hormone test system
Regulatory Class: II
Product Code: JLW
Dated: February 4, 2014
Received: February 7, 2014

Dear Ms. Loebel:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Courtney H. Lias -S

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement on last page.

510(k) Number *(if known)*
k131928

Device Name
FREND™ TSH

Indications for Use *(Describe)*

FREND™ TSH is designed for in vitro DIAGNOSTIC USE ONLY for the quantitative measurement of Thyroid Stimulating Hormone (thyrotropin or TSH) in human serum and lithium heparin plasma using the FREND™ system.

FREND™ TSH is indicated for use in clinical laboratories upon prescription by the attending physician as an aid to clinicians in the diagnosis of thyroid disease.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Yung W. Chan -S

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